REMARKS

Prior to this Amendment, claims 1-46 were pending in the present application. By this Amendment, claims 47-66 have been added. Accordingly, claims 1-66 are now pending.

According to the Office Action, the group restriction of a specifically named therapeutic agent as listed in claims 6-9, 15-18, 24-27, 33-36, 43-44 has been vacated and therefore all therapeutic agents listed in the above-identified claims are being examined in the pending application. In addition, the species restriction of a specifically named cationic polyelectrolyte as listed in claims 4, 13, 22, 31, and 41 has been withdrawn with respect to chitosan and gelatin and therefore the cationic polyelectrolytes of chitosan and gelatin are being examined in the present invention.

Claims 2, 3, and 10-46 have been indicated as being free of the prior art. Claims 1, 4-6, 9,10, 15, 19, 24 and 28-46 have been rejected and claims 2, 3, 11-14, 16-18, 20-23, and 25-27 have been objected to in the Office Action.

Objection to Claims 6, 15, 24, 33, and 43

According to the Office Action, claims 6, 15, 24, 33, and 43 have been objected to because "vascular ell growth promoters" should be written as "vascular cell growth promoters." Applicants have amended claims 6, 15, 24, 33, and 43 accordingly and therefore request withdrawal of this rejection.

Rejection of Claims 1, 6, 10, 15, 19, 24, 28, 33, 38, and 43

Claims 1, 6, 10, 15, 19, 24, 28, 33, 38, and 43 have been rejected under 35 U.S.C. §112 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, it appears that the Examiner objects to some of the terminology of the negatively charged therapeutic agents recited in claims 6, 15, 24, 33. In particular, the Examiner appears to take issue with the use of the terms anti-thrombogenic "agents," angiogenic "agents," anti-angiogenic agents, vascular cell

growth promoters, vascular cell growth inhibitors, cholesterol lowering "agents", vasodilating "agents", agents which interfere with endogenous vasoactive agents, "agents" that protect against cell death, cell cycle inhibitors, anti-restenosis "agents" and polynucleotides encoding such "agents."

As an initial matter, Applicants point out that according to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1" 'Written Description' Requirement" 66 FR 1099 (January 5, 2001), there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed.

Secondly, according to the PTO's written description guidelines, a lack of adequate written description does not arise if the knowledge and level of skill in the art would permit one skilled in the art to immediately envisage the product claimed from the disclosure. *See* 66 FR 1099, 1102. Applicants point out that the level of skill in the art is high with respect to the agents recited in claims 6, 15, 24, 33 for use in a coated implantable medical device. As such, Applicants are not claiming unknown or previously undescribed agents such as was the case in the case law the Examiner cites (*i.e., Fiers v. Revel and Regents of the Univ. Calif. v. Eli Lilly & Co.*)

Third, the agents recited in claims 6, 15, 24, 33 are not being claimed *per se* but are recited in dependent claims and are being claimed as part of a coating of an implantable medical device. As such, the Examiner's attention is drawn to In re Herschler, 200 USPQ 711 (CCPA 1979) which is cited by the Guidelines for the proposition that "'use of known compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.'" Applicants have specifically mentioned the class of compounds recited in claims 6, 15, 24, and 33 throughout the specification and in particular on page 9 and 10 and have recited in the claims that these agents all have the feature of being negatively charged. Thus, since the agents are auxiliary to the claimed medical devices and methods, these claims have an sufficient written description, according to the Guidelines.

Moreover, the facts of the present application resemble those in Herschler. In Herschler, the claims were directed to a method of enhancing the penetration of steroids across skin through the use of DMSO. The steroid was mixed with the DMSO and the penetration of the steroid across the skin was thereby enhanced through the action of the DMSO. The claims recited the broad class of steroids while the specification disclosed only a single species of steroid. The Board of Appeals found a lack of written description. The Court of Customs and Patent Appeals reversed. The court reasoned that the novelty of the invention was the use of DMSO to transport a broad category of substances across the skin. The success of the invention did not depend on the structure of any particular steroid; a large number of steroids would be expected to function in the invention. In view of this, the court held that detailed descriptions of the structures of numerous steroids were unnecessary. What was necessary was merely that the specification lead one of ordinary skill to the class of steroids. "In sum, claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds." (200 USPQ at 718).

The present claims are directed to medical devices and methods in which the therapeutic agents and their specific structures are auxiliary to the invention. The invention involves a medical device comprising alternating layers of cationic polyelectrolyte carriers and negatively charged therapeutic agents. One feature of this invention is the interaction between the positive charges on the carrier layer and the negative charges on the therapeutic agents. Like the steroids in Herschler, the present invention is disclosed as being capable of operating with a wide variety of therapeutic agents.

In view of these similarities, the Applicants submit that Herschler requires that the present specification be found to provide a sufficient written description for claims 1, 6, 10, 15, 19, 24, 28, 33, 38, and 43.

Fourth, the Applicants' description of the properties and functions of the recited negatively charged therapeutic agents would suggest to persons skilled in the art that the Applicants intend to claim "negatively charged therapeutic agents" broadly. In this regard, the

Examiner's attention is drawn to In re Smythe, cited by the Guidelines to describe that "the phrase 'air or other gas which is inert to the liquid' was sufficient to support a claim to 'inert fluid media' because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of 'inert fluid' broadly." Applicants have defined "negatively charged therapeutic agent" on page 6 of the specification as having the property of being "negatively charged, either naturally or synthetically" and provide numerous examples of such therapeutic agents throughout the specification and in particular on page 9 and 10.

For at least these reasons, Applicants believe there is sufficient written description for the term "negatively charged therapeutic agent" recited in claims 1, 6, 10, 15, 19, 24, 28, 33, 38, and 43 and for the specific negatively charged therapeutic agents recited in claims 6, 15, 24, 33.

The Applicants note that the Examiner stated that, with respect to the agents listed in claims 6, 15, 24, 33, and 43, the specification provides a sufficient written description for "anti-thrombogenic proteins (heparin, heparin derivatives, urokinase, and PPACK), antioxidant compounds (probucol and retinoic acid), angiogenic proteins, agents which block smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic/antiproliferative/anti-mitotic compounds, anti-microbial compounds, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, vascular cell growth antibody inhibitors, cholesterol lowering drugs, vasodilating drugs, proteins that protect against cell death, cell cycle CDK protein inhibtors, anti-restenosis proteins, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding any of the above named proteins" (Office Action, page 3, lines 4-11). Accordingly, solely in the interest of expediting the issuance of this subject matter and thus in no way conceding the correctness of the written description rejection discussed above, new claims 47-61 have been added. These new claims recite the above-listed agents and thus the Applicants submit that this written description rejection is not applicable to new claims 47-61.

Rejection of Claims 1, 6, 10, 15, 19, 24, 28, 33, 36, 38 and 43

Claims 1, 6, 10, 15, 19, 24, 28, 33, 36, 38, and 43 have been rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement (see the Office Action, paragraph bridging pages 4-5).

The Examiner did not provide reasons for this enablement rejection but stated that the claims were enabled for "anti-thrombogenic proteins, antioxidant compounds, angiogenic proteins, agents which block smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic/antiproliferative/anti-mitotic compounds, anti-microbial compounds, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, vascular cell growth antibody inhibitors, cholesterol lowering drugs, vasodilating drugs, proteins that protect against cell death, cell cycle CDK protein inhibtors, anti-restenosis proteins, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding any of the above named proteins" (Office Action, page 5, lines 1-7). The Applicants note that new claims 47-61 recite these agents. Accordingly, the Applicants submit that this enablement rejection is not applicable to new claims 47-61.

The U.S. Patent and Trademark Office bears the burden of making out a *prima facie* case of non-enablement (In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971)). In view of the lack of reasons provided for this rejection of claims 1, 6, 10, 15, 19, 24, 28, 33, 36, 38 and 43 (see the Office Action, paragraph bridging pages 4-5), the Applicants submit that such a *prima facie* case has not been made with respect to this enablement rejection.

Moreover, the specification does enable the full scope of these claims, in particular with respect to the therapeutic agents. As the specification indicates, making the therapeutic agents negatively charged "is routinely made by one skill in the art." See page 9, lines 10-12. Furthermore, exemplary methods of how to coat an implantable medical device according to the present invention are described in detail in the specification including, *inter alia*, Example 6 on page 16; Example 7 on page 17; Example 8 on page 17, and Example 10 on page 19.

This invention is not directed to an unpredictable area of technology such as "gene therapy," a term commonly used in the Office Action. This invention is directed to coated implantable medical devices and methods of making the same, where the level of skill in the art is high and the level of predictability is also high. Applicants need not recite every possible example of an angiogenic agent, a vascular cell growth promoter, an anti-thrombogenic agent, etc in order for the claims to these agents to be enabled since examples of such agents are well known in the art for use with an implantable medical device. Indeed, as stated in the MPEP, "a patent need not teach, and preferably omits, what is well known in the art." `(MPEP § 2164.01 (citing e.g. *In re Buchner*, 929 F.2d 660,661 (Fed Cir. 1991). Applicants respectfully submit that the Examiner has not meet the burden of establishing a reasonable basis to question the enablement provided for the claimed invention. Therefore, Applicants respectfully request withdrawal of the rejection to claims 1, 6, 10, 15, 19, 24, 28, 33, 36, 38, and 43.

Rejection of Claims 28-46

Claims 28-46 have been rejected because the claims as written do not necessarily limit the location to a described location or target tissue in a mammal. According to the Examiner, because the specification only teaches that in order to employ the claimed medical device within applicant's framework of the invention, it is necessary to implant the claimed medical device to a desired target tissue in a mammal and that it is not apparent how one skilled in the art practices the full breadth of the claimed methods on the basis of the applicant's disclosure. Applicants have provided several non-limiting examples of target sites in the specification including the heart, lung, brain, liver, skeletal muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostrate, cartilage, and bone (See page 13, lines 16-20). Applicants have also provided several non-limiting examples of the types of disease or tissue or organ dysfunction the methods of the invention can be used for (see page 13, lines 22-25 to page 14, lines 1-6). Applicants have also provided an example of the delivery of an implantable medical device as recited in the claims in the heart (see Example 11, page 20). Once again, Applicants submit that the level of skill in the relevant art is high with respect to the present invention, and that one skilled in the art would

know what target location to implant the medical device recited in the claims depending on which disease or tissue or organ dysfunction is desired to be affected. Only for the purpose of furthering prosecution in the present case, however, Applicants have amended independent claims 28 and 38 to recite a "target location in a mammal."

Beginning at the bottom of page 6 and extending to the top of page 9 of the Office Action, the Examiner argued that claims 28-46 read on methods of gene therapy and cited several publications which allegedly support the proposition that these claims lack enablement.

Once again, the Applicants would like to stress that their invention should not be characterized as "gene therapy." The present invention instead is directed to coated implantable medical devices and methods of making the same, where the level of skill in the art is high and the level of predictability is also high. Claims of the present invention involve a medical device comprising alternating layers of cationic polyelectrolyte carriers and negatively charged therapeutic agents, which affords substantial benefits over previous coated medical devices. As explained below, this contribution is novel and non-obvious over the prior art and consequently, the Applicants are entitled to broadly claim their invention.

The publications cited by the Examiner have essentially no relevance to the field of coated medical devices. None of the references even discusses medical devices such as stents or catheters. Moreover, the Examiner's treatment of these publications suffers from a general flaw. The Examiner's analysis focuses entirely on the negative aspects of these publications, i.e., the potential problems discussed. There is no mention of the fact that the these publications often discuss a potential problem and then go on to disclose how that problem can be solved or avoided. For example, with respect to the problem of targeting specific cell types for retroviral vector entry, *Anderson*, discusses approaches such as "tethering" that have been successful in concentrating the vector in the extracellular matrix in the vicinity of target cells. *(See Anderson*, page 26).

The skilled artisan, when practicing the invention, does not operate in a vacuum. There is a specific goal in mind; a specific disease or condition that is intended to be treated. The skilled artisan would know that certain approaches are to be pursued and others avoided, given the

specific goal in mind. The Examiner appears to believe that the skilled artisan is reduced to experimenting blindly, trying one thing after another in hopes that something will work. If this were true, perhaps undue experimentation might be necessary to practice the invention. But this is not true, even with respect to gene therapy. As shown below, there is ample guidance to be found in the knowledge in the art such that this can be avoided. Such guidance ensures that the invention can be practiced without undue experimentation.

Even if the Examiner is correct that publications relating to gene therapy have relevance with respect to the question of the enablement of the present claims, the scientific literature indicates that gene therapy at the time of the filing of the present application was a much less dubious undertaking than the Examiner thinks. A search of the biomedical literature was conducted on PubMed (http ://www.ncbi.nlm.nih.gov/entrez/query.fcgi). The search covered the time period from one year before up to the filing date of the present application, i.e., January 2, 2000 through January 2, 2001. The search was directed to those publications in which the phrase "gene therapy" appeared in the title or abstract. More than 3,000 hits were obtained. A copy of a printout of the search terms and the titles of the first 100 hits is enclosed as Exhibit A.

Examination of the abstracts of those first 100 hits revealed at least 9 publications that, judging from the abstracts, reported success in the use of gene therapy in mammals. For example:

- Nasu et al., 2001, Prostate Cancer Prostatic. Dis. 4:44-55 reported success in the use of adenoviral based gene therapy in a mouse model of prostate cancer.
- Jindal et al., 2001, Int. J. Exp. Diabetes Res. 2:129-138 reported the prevention of diabetes in a mouse model of diabetes by the an adeno-associated viral delivery of the insulin gene.
- Herzog & Hagstrom, 2001, Am. J. Pharmacogenomics 1:137-144 reported that the year 2000 saw the first successful treatment of a genetic disease in humans by gene therapy. The authors also stated that various clincal trials were in progress involving the use of gene therapy to treat various types of hemophilia.
- Francis et al., 2001, Am. J. Pharmacogenomics 1:55-66 referred to "promising results in human and animal gene transfer studies" for cardivascular diseases.

- Oyama et al., 2000, Mol. Urol. 4:83-87 reported the results of experiments using herpes vectors to treat urologic neoplasms and stated: "Our data suggest that G207 [a herpes vector] may be applicable for the treatment of urologic malignant tumors."
- Shirakawa et al., 2000, Mol. Urol. 4:73-82 reported that: "We have demonstrated the utility of two prostate cancer-specific promoters, long PSA and osteocalcin, for tisue-specific toxic gene therapy for prostate cancer."
- Irie et al., 2000, Mol. Urol. 4:61-66 reported that: "Mutated H-ras, fos, and erb-B2 genes have been chosen as targets for ribozymes in previous studies, and antitumor efficacy has been demonstrated by reversion of the malignant phenotypes and by inhibition of tumor growth both in vitro and in vivo."
- Kawai et al., 2000, Mol. Urol. 4:43-46 reported that, for renal cell carcinoma and prostate cancer, "Transduction of the gene encoding granulocyte-macrophage colony-stimulating factor has shown promise in preclinical studies, and clinical trials are in their early stages."
- Wilczyska et al., 2000, Acta Biochim. Pol. 48:1077-1084 reported that the delivery of angiostatin and interleukin-12 had a "synergistic therapeutic effect" in mouse models of neoplastic diseases.

Copies of the abstracts of those 9 publications reporting success are enclosed as Exhibit B. Extrapolating these findings to the over 3,000 hits of the search suggests that the scientific literature contained more than 270 reports of the successful use of gene therapy in mammals in just the one year period leading up to the filing of the present application. Assuming that the art of gene therapy is relevant to the present invention, these publications, and similar publications from prior years, would have provided a rich source of guidance for one skilled in the art and would have ensured that the present invention could be practiced without undue experimentation.

At page 5, lines 12-23, of the Office Action, the Examiner stated that the specification is enabling for claims limited to:

> A method of delivering a therapeutic agent to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 28 at a desired location or tissue in a mammal, wherein the coating comprises a therapeutic agent;

> A method of delivering a DNA encoding a protein to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 38 at a desired location or tissue in a mammal, wherein the coating comprises a polynucleotide encoding a protein;
>
> A method of delivering a DNA encoding a therapeutic protein to a mammal, the method comprising implanting a medical device comprising the coating as recited in claim 38 at a desired location or tissue in a mammal, wherein the coating comprises a polynucleotide encoding a protein selected from the group consisting of anti-thrombogenic proteins, angiogenic proteins, vascular cell growth promoting proteins, vascular cell growth protein inhibitors, proteins that protect against cell death, cell cycle CDK protein inhibtors, anti-restenosis proteins, and bone morphogenic protein.

Accordingly, solely in the interest of expediting the issuance of this subject matter and thus in no way conceding the correctness of the enablement rejection discussed above, new claims 62-64 have been added. These new claims have been drafted along the lines of the above-described subject matter said to be enabled by the Examiner. Consequently, the Applicants submit that the enablement rejection is not applicable to new claims 62-64.

At page 7, lines 1-4, of the Office Action, the Examiner indicated certain subject matter that the Examiner stated is enabled:

> Other than a sufficient enablement of direct administration of an anti-proliferative gene to inhibit restenosis or the growth of tumor cells in a mammal, and of a DNA coding for an angiogenic factor to induce the growth of clood vessels at a site of the local delivery of the DNA, as indicated in the specification and state of the prior art of record ...

Solely in the interest of expediting the issuance of this subject matter and thus in no way conceding the correctness of the enablement rejection discussed above, new claims 65-66 have been added. These new claims have been drafted along the lines of the above-described subject matter said to be enabeled by the Examiner. Consequently, the Applicants submit that the enablement rejection is not applicable to new claims 65-66.

Rejection of Claims 28-38

Claim 28 has been rejected under 35 U.S.C. 112, second paragraph as being indefinite because the term "near" is a relative terminology and does not exactly define the intended metes and bounds of the "near the target location." Applicants do not agree with that characterization but to advance prosecution of the respective claim, Applicants have deleted the term "near" from claim 28.

Rejection of Claims 37 and 46

Claims 37 and 46 have been rejected because the recitation of "urethra malignant growth or benign growth are indefinite because it is not apparent how a growth of urethra can be a structural location or tissue at which the claimed medical device can be implanted. For the purpose of clarification, Applicants intend to recite the target location as being any of the target locations recited in claims 37 and 46 including areas of those target locations in which benign and malignant growths have developed.

Rejection of Claim 1 under 35 U.S.C. §102(e)

Claim 1 has been rejected under 35 U.S.C. §102(e) as being allegedly anticipated by U.S. Patent No. 6,044,943 to Shi ("Shi"). Applicants have amended claim 1 to remove the recitation of "optionally." Applicants submit that Shi does not teach or suggest an implantable medical device comprising "additional layers or layers of cationic polyelectrolyte carrier and an additional layer or layers of at least one negatively charged therapeutic agent adsorbed onto said additional layers or layers of cationic polyelectrolyte carrier, wherein said additional layer or layers of polyelectrolyte carrier and said additional layer or layers of negatively charged therapeutic agent alternate." Applicants therefore submit that claim 1 is not anticipated by Shi and respectfully request withdrawal of this rejection.

Rejection of Claims 1, 4-6, and 9 Under 35 U.S.C. §103(a)

Claims 1, 4-6, and 9 have been rejected under 35 U.S.C. §103(a) as being allegedly rendered obvious by U.S. Patent No. 5,578,073 to Haimovich ("Haimovich") in view of Shi and U.S. Patent No. 6,013,780 to Neufeld ("Neufeld"). Applicants submit that a *prima facie* case of obviousness has not been established as none of the cited references teach or suggest an implantable medical device comprising "additional layers or layers of cationic polyelectrolyte carrier and an additional layer or layers of at least one negatively charged therapeutic agent adsorbed onto said additional layers or layers of cationic polyelectrolyte carrier, wherein said additional layer or layers of polyelectrolyte carrier and said additional layer or layers of negatively charged therapeutic agent alternate," which is a recitation of claim 1. Moreover, there is no evidence in the references themselves or in the knowledge generally available to one of skill in the art that any of the references could or should be modified to meet this recitation of claim 1. For example, there is no indication that the references or the knowledge of one skilled in the art appreciate that alternating layers of cationic polyelectrolyte carriers and negatively charged therapeutic agent increase the amount of therapeutic agent adsorbed onto the medical device and provide for a controlled release of the negatively charged therapeutic agent, as taught by the present invention (See specification, page 7, lines 13-18). For at least this reason, Applicants submit that claims 1, 4-6, and 9 are not rendered obvious by any of the cited references and therefore respectfully request withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicant's representative to discuss any issue that would expedite allowance of the subject application.

It is not believed that any extensions of time or other fees are required in connection with the filing of this response. However, if any fees for extension(s) of time or additional fees are required in connection with the filing of this response, such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,
KENYON & KENYON

Dated: March 6 2003 By: _____

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MARKED-UP VERSION SHOWING CHANGES MADE

1. An implantable medical device comprising [an implantable medical device having] a coating on at least one portion of at least one surface, said coating comprising:

an inner layer of a cationic polyelectrolyte carrier; and

a layer of at least one negatively charged therapeutic agent adsorbed onto said inner layer of cationic polyelectrolyte carrier; and

[optionally,] an additional layer or layers of cationic polyelectrolyte carrier and an additional layer or layers of at least one negatively charged therapeutic agent adsorbed onto said additional layer or layers of cationic polyelectrolyte carrier, wherein said additional layer or layers of polyelectrolye carrier and said additional layer or layers of negatively charged therapeutic agent alternate.

6. The medical device of claim 1, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic agents, antioxidants, angiogenic agents, anti-angiogenic agents, agents capable of blocking smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic agents, antiproliferative agents, anti-mitotic agents, anti-microbials, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, agents that protect against cell death, cell cycle inhibitors, anti-restenosis agents, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding such agents.

15. The method of claim 10, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic agents, antioxidants, angiogenic agents, anti-angiogenic agents, agents capable of blocking smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic agents, antiproliferative agents, anti-mitotic agents, anti-microbials, anesthetic

agents, nitric oxide donors, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, agents that protect against cell death, cell cycle inhibitors, anti-restenosis agents, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding such agents.

24. The medical device of claim 19, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic agents, antioxidants, angiogenic agents, anti-angiogenic agents, agents capable of blocking smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic agents, antiproliferative agents, anti-mitotic agents, anti-microbials, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, agents that protect against cell death, cell cycle inhibitors, anti-restenosis agents, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding such agents.

28. A method of delivering a therapeutic agent to a target location by implanting in [or near] the target location in a mammal a medical device comprising a negatively charged therapeutic agent adsorbed on the surface thereof; wherein the medical device is produced by a process comprising:

(a) coating at least one portion of at least one surface a medical device with a cationic polyelectrolyte carrier to form a layer of cationic polyelectrolyte carrier;

(b) washing the layer of cationic polyelectrolyte carrier with a washing solution;

(c) adsorbing one or more negatively charged therapeutic agent onto the layer of cationic polyelectrolyte carrier to form a layer of therapeutic agent; and optionally

(d) washing the layer of therapeutic agent with a washing solution and repeating steps (a) through (c) one or more times to form multiple layers of cationic polyelectrolyte carrier

and therapeutic agent until a desired amount of therapeutic agent has been adsorbed onto the medical device.

33. The method of claim 28, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic agents, antioxidants, angiogenic agents, anti-angiogenic agents, agents capable of blocking smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic agents, antiproliferative agents, anti-mitotic agents, anti-microbials, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, agents that protect against cell death, cell cycle inhibitors, anti-restenosis agents, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding such agents.

37. The method of claim 28, wherein the target location comprises at least one location selected from the group consisting of brain, heart, liver, skeletal muscle, smooth muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostate, cartilage, bone, lung, blood vessel, ureter, urethra, and testes [urethra malignant growth, or benign growth].

38. A method for treating or reducing the occurrence or severity of a clinical disease or condition, comprising:

(a) preparing a medical device by:

(i) coating at least one portion of at least one surface a medical device with a cationic polyelectrolyte carrier to form a layer of cationic polyelectrolyte carrier;

(ii) washing the layer of cationic polyelectrolyte carrier with a washing solution;

(iii) adsorbing one or more negatively charged therapeutic agent effective to treat or reduce the occurrence of the clinical disease or condition onto the layer of cationic polyelectrolyte carrier to form a layer of therapeutic agent; and optionally

(iv) washing the layer of therapeutic agent with a washing solution and repeating steps (i) through (iii) one or more times to form multiple layers of cationic polyelectrolyte carrier and therapeutic agent until a desired amount of therapeutic agent has been adsorbed onto the medical device.

(b) implanting the medical device into a target location in a mammal from which the therapeutic agent can treat or reduce the occurrence or severity of the clinical disease or condition.

43. The method of claim 38, wherein at least one of the one or more negatively charged therapeutic agent comprises at least one agent selected from the group consisting of anti-thrombogenic agents, antioxidants, angiogenic agents, anti-angiogenic agents, agents capable of blocking smooth muscle cell proliferation, anti-inflammatory agents, calcium entry blockers, antineoplastic agents, antiproliferative agents, anti-mitotic agents, anti-microbials, anesthetic agents, nitric oxide donors, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol lowering agents, vasodilating agents, agents which interfere with endogenous vasoactive mechanisms, agents that protect against cell death, cell cycle inhibitors, anti-restenosis agents, agents for treating malignancies, bone morphogenic proteins, and polynucleotides encoding such agents.

48. The method of claim 38, wherein the target location comprises at least one location selected from the group consisting of brain, heart, liver, skeletal muscle, smooth muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostate, cartilage, bone, lung, blood vessel, ureter, urethra, [ovary,] and testes[, malignant growth, or benign growth].